REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims

Pending claims

Claims 1 to 5, 7 to 25, 28 to 34, 36 to 61, 63 to 74, 96 to 114, 116 to 127 and 129 to 133 are pending in the application.

Outstanding Rejections

Claims 25, 29, 31, 33, 34, 36 and 37 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Queen et al. USPN 5,693,762. Claims 25 and 29 to 31, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bendig et al. USPN 5,558,864. Claims 25, 28, 29, 31, 33, 34, 36 and 37, are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Baca et al. USPN 6,884,879. Claims 1 to 5, 7 to 25, 28 to 34, 36 to 61, 63 to 74, 96 to 114, 116 to 127 and 129 to 133, are newly rejected as allegedly not complying with 35 U.S.C. §112, first paragraph, written description requirement. Applicants respectfully traverse all outstanding rejections of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the claims as amended in this and previous responses. For example, support for claims encompassing methods comprising comparing the HVR1 and/or HVR2 amino acid sequences of a non-human antibody with a corresponding HVR1 and/or HVR2 of human consensus subgroups for the heavy or light chain, identifying the human variable domain subgroup consensus sequence with the most identity to that HVR1 and/or HVR2 amino acid sequence of the non-human antibody, and selecting at least one of the FRs of that subgroup consensus sequence as the FR sequence for the recombinant antibody or antigen binding fragment, can be found inter alia in the sentence spanning pages 4 to 5, of the specification, which is paragraph [0013] of this application's publication U.S. Pat App Pub.

No. 20040229310 ("the '310 publication"). Accordingly, no new matter has been added and the amendment should be properly entered.

No new matter has been added by the addition of the new claims or the amendments. Entry of the amendments is respectfully requested. With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any subject matter not presently claimed in one or more future or pending continuation and/or divisional applications.

Applicants respectfully request entry of the amendments set forth in this response under 37 CFR §1.116. The amendment places the case in condition for allowance and places the case in better condition for appeal; the amendment does not raise any issues of new matter; and, the amended and/or new claims do not present new issues requiring further consideration or search.

Issues under 35 U.S.C § 102

Queen et al. USPN 5,693,762, and §102(b)

Claims 25, 29, 31, 33, 34, 36 and 37, are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Queen et al. USPN 5,693,762, issued December 2, 1997, filed June 7, 1995 (hereinafter "Queen"), for reasons set forth in paragraph 5, pages 2 to 5, of the OA.

In brief, the Office alleges *inter alia* that Queen teaches comparing framework (FR[1]) or hypervariable region (HVR, or CDRs[2]) sequences of a "donor" (non-human) antibody to corresponding sequences from a collection of (human) consensus sequences, citing in particular column 2, lines 40 to 45 of Queen:

> The preferred methods comprise first comparing the framework or variable region amino acid sequence of the donor immunoglobulin to corresponding sequences in a collection of human immunoglobulin chains, and selecting as the human immunoglobulin one of the more homologous sequences from the collection.

[1] See the definition of FR in the specification on page 21, line 26, to page 22, line 6; paragraph [0066] of the '310 publication

[2] See the definition of HVR and CDR in the specification on page 21, lines 12 to 25; paragraph [0065] of the '310 publication.

However, in contrast to the instant claimed methods, Queen compares "donor" (non-human) framework (FR) sequence to "acceptor" (human) FR sequence (or variable region to variable region) to determine which human immunoglobulin will be selected (sequences from the non-human antibody responsible for antigen binding are then implanted into the selected human antibody). For example, see e.g. Example 6, column 55, lines 30 to 50, where Queen describes comparing FR sequences between a mouse antibody and a database of human sequences, and using that FR to FR comparison to determine which FR sequences in the donor to insert in the FR of the acceptor human antibody.

In contrast to Queen, as summarized by the Office on page 3, lines 22 to 27, of the OA, the claimed methods of this invention compare HVR sequence with other HVR sequences in the selection of FR amino acid residues to use in the Ab humanization process.

The Office alleges that step (iii) of the instant claim 25 "inherently or implicitly" used FR region sequence to select which FR sequence to use in the humanization process, see e.g., page 4, lines 8 to 16, of the OA. However, clearly step (iii) of the instant claim 25 does not explicitly compare FR region sequence to FR region sequence to select a human subgroup variable domain consensus sequence from which an FR sequence is selected to use in the humanization process:

> (iii) identifying at least one amino acid position in at least one framework region (FR) of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than that of a corresponding position in a FR of the variable domain or antigen binding fragment of the non-human antibody;

nor is this Applicants' intent for the claimed invention[3]. The selection of FR amino acid residue(s) in step (iii) occurs only after a human subgroup variable domain consensus sequence is selected by HVR to HVR comparison (step (ii)).

The instant amendment also addresses this issue by clarifying that the instant claim 25 does not explicitly or "inherently or implicitly" compare FR sequence to FR sequence for the purpose of selecting a human subgroup variable domain consensus sequence (from which FR residue(s) are selected) for use in the humanization process:

> (ii) selecting a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence;

[3] As acknowledged by the OA on page 3, lines 22 to 27, of the OA.

> (iii) identifying at least one amino acid position in at least one framework region (FR) of the ~~selected~~ human subgroup variable domain consensus sequence selected in step (ii) that has a different amino acid residue than that of a corresponding position in a FR of the variable domain or antigen binding fragment of the non-human antibody ...

This amendment to claim 25 has step (iii) explicitly only using FR sequence from a human subgroup variable domain consensus sequence selected by comparing HVR1 and/or HVR2 amino acid sequence.

Accordingly, in light of these Remarks and the instant amendment, the section 102(b) rejection based on Queen should be properly withdrawn.

Bendig et al. USPN 5,558,864, and §102(b)

Claims 25 and 29 to 31, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bendig et al. USPN 5,558,864[4], issued September 24, 1996, filed March 4, 1992 (hereinafter "Bendig"), for reasons set forth in paragraph 6, pages 5 to 7, of the OA.

As with Queen, the Office alleges that step (iii) of the instant claim 25 "inherently or implicitly" compared FR region sequence to select FR sequence, see e.g., the last paragraph of page 6, of the OA. However, as noted above, step (iii) does not explicitly compare FR region sequence to FR region sequence to select a human subgroup variable domain consensus sequence from which an FR sequence is selected to use in the humanization process. The instant amendment also addresses this issue by clarifying that the instant claim 25 does not explicitly or "inherently or implicitly" compare FR sequence to FR sequence for the purpose of selecting a human subgroup variable domain consensus sequence (from which FR residue(s) are selected) for use in the humanization process.

Accordingly, in light of these Remarks and the instant amendment, the section 102(b) rejection based on Bendig should be properly withdrawn.

Baca et al. USPN 6,884,879, and §102(e)

Claims 25, 28, 29, 31, 33, 34, 36 and 37, are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Baca et al. USPN 6,884,879, issued April 26, 2005, filed August 06, 1997

(hereinafter "Baca, USPN 6,884,879"), as evidenced by Queen, for reasons set forth in paragraph 7, pages 7 to 9, of the OA.

As with Queen and Bendig, the Office alleges that step (iii) of the instant claim 25 "inherently or implicitly" compared FR region sequence to select FR sequence, see e.g., the paragraph spanning pages 8 to 9, of the OA. However, as noted above, step (iii) does not explicitly compare FR region sequence to FR region sequence to select a human subgroup variable domain consensus sequence from which an FR sequence is selected to use in the humanization process. The instant amendment also addresses this issue by clarifying that the instant claim 25 does not explicitly or "inherently or implicitly" compare FR sequence to FR sequence for the purpose of selecting a human subgroup variable domain consensus sequence (from which FR residue(s) are selected) for use in the humanization process.

Accordingly, in light of these Remarks and the instant amendment, the section 102(e) rejection based on Baca should be properly withdrawn.

Issues under 35 U.S.C. §112, first paragraph, written description

Claims 1 to 5, 7 to 25, 28 to 34, 36 to 61, 63 to 74, 96 to 114, 116 to 127 and 129 to 133, are newly rejected as allegedly not complying with 35 U.S.C. §112, first paragraph, written description requirement, for reasons set forth in detail on pages 9 to 13, of the OA.

Applicants thank the Office for acknowledging embodiments of this invention enabled by this application's specification's disclosure, see from the sentence spanning pages 9 to 10, to line 9, of page 11, of the OA.

However, the Office alleges *inter alia* that the specification does not describe methods of modifying any one amino acid at the corresponding position of any and all non-human variable domains of the antibody or antibody binding fragment; in particular, it is alleged that there is no disclosure for aligning any light chain hypervariable region 1 (HVR1) and/or a light chain hypervariable region 2 (HVR2) of a variable domain of any non-human antibody or antigen binding fragment thereof to corresponding light chain HVR1 or HVR2 sequences of human subgroup variable domain consensus sequences (see e.g., page 11, lines 10 to 19, of the OA).

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[4] USPN 5,558,864 is correct, the Office confirmed that USPN 5,558,564 is a typo (as discussed in a telephonic interview June 11, 2008; this interview summarized in Applicants' response of July 17, 2008).

In fact, there is express support for this embodiment (see e.g., the sentence spanning pages 4 to 5, of the specification, or paragraph [0013] of the '310 publication):

> [0013] In other embodiments, a method comprises comparing the HVR1 and/or HVR2 amino acid sequence of the non-human antibody with the corresponding HVR1 and/or HVR2 of the human consensus subgroups for the heavy or light chain, identifying the human variable domain subgroup consensus sequence with the most identity to that HVR1 and/or HVR2 amino acid sequence of the non-human antibody, and selecting at least one of the FRs of that subgroup consensus sequence as the FR sequence for the recombinant antibody or antigen binding fragment.

The claimed methods of this invention compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of human subgroup variable domain consensus sequences from which FR amino acid residues are selected to use in the Ab humanization process. In brief, HVR sequences are used to select which human subgroup variable domain consensus sequences, and thus which human FR amino acids, will be used in the Ab humanization process. FR sequences are not used in the selection of human subgroup variable domain consensus sequences, only HVR sequence are used (e.g., mouse HVR to human HVR). FR sequence is not used to select which human subgroup variable domain consensus sequences (and thus which human FR residues) are substituted into a non-human FR.

The Office also alleges *inter alia* that the specification does not describe modifying any particular FR amino acid residue position other than the specific residue changes set forth for the anti-VEGF antibody in e.g. claims 19 to 21, or claims 52 to 54, 56, 57, 63 or 64, that would improve the yield of antibodies (made in a host cell); see e.g., page 11, lines 19 to 23, of the OA.

Applicants emphasize that this application is not claiming compositions such as modified antibodies made by the methods of this invention. Pending claims are only directed to methods for modifying antibody sequence, and the specification provides express disclosure as to how to select FR residues for modification; for example, as noted above in the sentence spanning pages 4 to 5, of the specification. See also e.g., page 5, lines 10 to 16, of the specification, or paragraph [0014] of the '310 publication):

> ... A method comprises expressing a variable domain of the antibody or antigen binding fragment comprising at least one modified FR in a host cell, wherein the modified FR has a substitution of at least one amino acid position with a different amino acid, wherein the different amino acid is the amino acid found at the corresponding FR position of a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid

> sequence with the most sequence identity with a corresponding HVR1 and/or HVR2 sequence of the variable domain, ...

The embodiment of the invention as set forth in claim 100, more specifically describes the variable domain residues to be modified as (i) a substitution of at least one but not all amino acids proximal to a cysteine (cys) reside that participates in an intrachain variable domain disulfide bond with a different amino acid, or (ii) deleting at least one but not all amino acids proximal to a cys reside that participates in an intrachain variable domain disulfide bond.

Citing Wu (1999) JMB 294:151-162, the Office also expressed concerns that changing FR amino acid positions may adversely effect an antibody's binding specificity, alleging it would take undue experimentation to determine which FR amino acid residue changes would tolerate change and which would not (see e.g. page 12, lines 3 to 6, of the OA). From a written description perspective, the specification has given clear direction to the skilled artisan regarding which non-human FR residues are to be substituted with human FR residues to practice the claimed methods.

From an enablement perspective, it would not take undue experimentation to determine which products of the claimed methods retain antigen binding activity. Whether large numbers of compositions (including antibodies) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue." The Federal Circuit in In re Wands directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation.

The facts in In re Wands are sufficiently analogous to the instant application to help illustrate this point, as explained in MPEP §2164.06(b), pg 2100-197, 8th ed., rev. 7, July 2008:

> (B) In In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court reversed the rejection for lack of enablement under 35 U.S.C. 112, first paragraph, concluding that undue experimentation would not be required to practice the invention. The nature of monoclonal antibody technology is such that experiments first involve the entire attempt to make monoclonal hybridomas to determine which ones secrete antibody with the desired characteristics. The court found that the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, that all of the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. Furthermore, the applicant carried out the entire procedure for making a monoclonal antibody against HBsAg three times and

> each time was successful in producing at least one antibody which fell within the scope of the claims.

In In re Wands, after considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407. In In re Wands, it was not necessary to provide a method to routinely identify *every* monoclonal antibody hybridoma made in any particular production round, or *every possible* monoclonal antibody that could bind the exemplary antigen. Nor was it necessary to produce a working specie after very antibody-making procedure. In fact, in In re Wands, the screening protocol was found sufficiently enabling even though only one antibody was identified after running three procedures. See also MPEP §2164.08(b), pg 2100-205, 8th ed., rev. 7, July 2008, noting that the presence of inoperable embodiments within the scope of claim does not necessarily render a claim nonenabled.

This invention is analogous to In re Wands, as it also involves screening antibodies for activity; thus, for this invention one of skill in the art using the teaching of the specification could without undue experimentation have determined if an antibody made by the claimed methods, having increased folding efficiency and yields, also had retained antigen binding activity.

To support the lack written description (WD) allegation, the Office cites case law (including for example *Eli Lilly* and *Vas-Cath v Mahurkar*, the MPEP and the USPTO written description guidelines (see e.g. page 12, line 7 to page 13, line 20, of the OA). However, the holding of these cases apply to WD for claiming genuses of compositions; in contrast, this application only claims methods for making antibodies.

Also illustrative is the cited USPTO WD guidelines for Examiners, where Example 16 teaches that when a process is claimed where the novelty resides in the process steps, it is the degree of predictability and level of skill in the art that (amongst other factors) that is used to determine whether the process claim meets section 112's WD requirement (in Example 16, the method for introducing a nucleic acid into the mitochondria of a mammalian cell was found to comply with section 112's WD requirement). Analogously, this application claims processes where the novelty resides in the process steps, and because the claimed methods predictably produce antibodies having improved folding efficiencies and yields, one of skill in this art would recognize the inventors were in possession of these claimed methods.

Finally, although the Office is concerned about whether the modified antibodies made by the claimed methods retain the same or similar antigen binding capability as the corresponding unmodified antibody, please note there is no limitation in the pending claims that these modified antibodies need have the same or similar antigen binding capability as the corresponding unmodified antibody; it is only necessary that the claimed methods produce antibodies having improved folding efficiencies and yields.

Accordingly, in light of these Remarks and the instant amendment, the rejection under section 112's WD requirement should be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly enter the amendments set forth in this response under 37 CFR §1.116, and can properly withdraw the rejection of the pending claims under 35 U.S.C. §102(b), 35 U.S.C. §102(e) and 35 U.S.C. §112, first paragraph. In view of the above, all claims pending in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 146392004900. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has review the instant response and amendment, please telephone the undersigned at (858) 720-5133.

Dated: January 13, 2009

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